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Mizoroki–Heck Cyclizations of Amide Derivatives for the Introduction of Quaternary Centers

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Abstract: *We report non-decarbonylative Mizoroki–Heck reactions of amide derivatives. The transformation relies on the use of nickel catalysis and proceeds using sterically hindered tri- and tetrasubstituted olefins to give products containing quaternary centers. The resulting polycyclic or spirocyclic products can be obtained in good yields. Moreover, a diastereoselective variant of this method gives access to an adduct bearing vicinal, highly substituted sp^3 stereocenters. These results demonstrate that amide derivatives can be used as building blocks for the assembly of complex scaffolds.*

The introduction of quaternary carbon centers remains a popular topic in modern chemical synthesis.[1] Such motifs are often difficult to access owing to the steric challenge associated with constructing a fully substituted carbon center. One attractive means to install quaternary centers is the intramolecular Mizoroki–Heck reaction.[2] Most notably, the Pd-catalyzed Mizoroki–Heck cyclization of aryl halides and triflates has been the subject of intense investigation for decades and has been utilized to assemble many sterically demanding scaffolds. On the other hand, the corresponding Mizoroki–Heck cyclization of acyl electrophiles to furnish ketone products bearing quaternary carbon centers has not been reported.

Considering the aforementioned deficiency concerning the Mizoroki–Heck cyclization of acyl electrophiles, we pursued the transformation shown in Figure 1. In the presence of an appropriate nickel catalyst, imides **1**, derived from the corresponding secondary amide through Boc-activation, should be converted into cyclized products **2**, which bear the desired quaternary centers. Mechanistically, the conversion would proceed through a sequence akin to classical Mizoroki–Heck chemistry, involving oxidative addition (**1**→**3**), olefin coordination and insertion (**3**→**4**), and β-hydride elimination[3] (**4**→**2**). It should be noted that amide derivatives have recently been employed in Pd- and Ni-catalyzed couplings for carbon–heteroatom[4] and carbon–carbon[5–7] bond formation, although never for the synthesis of quaternary centers.[8] Moreover, precedent for the desired olefin insertion is available from Stambuli's Pd-catalyzed Mizoroki–Heck cyclization of benzoic anhydrides, albeit without the formation of a quaternary stereocenter,[9,10] and from Pd-catalyzed carbonylative Mizoroki–Heck reactions of aryl halides and triflates.[11] Herein, we describe the development and scope of a Ni-catalyzed Mizoroki–Heck cyclization of amide derivatives.[12] The transformation provides a new means to build complex scaffolds by using non-precious-metal catalysis.[13]

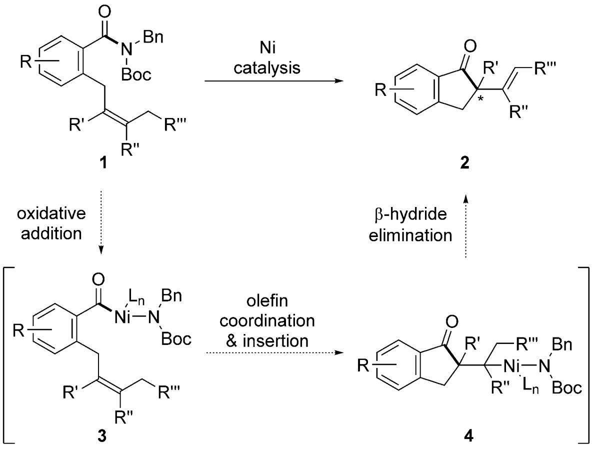

Figure 1. Nickel-catalyzed Mizoroki–Heck reaction of amide derivatives to create quaternary centers. Boc = *tert*-butyloxycarbonyl, Bn = benzyl.

After some initial experimentation, we arrived at **5** as a suitable test substrate (Table 1).[14] This substrate contains the *N*-Bn,Boc imide motif,[15] which we have previously found to be reactive using Ni/SIPr (**7**) combinations,[4,5] in addition to a sterically encumbered tetrasubstituted olefin. The Mizoroki–Heck cyclization of **5** was attempted under a variety of reaction conditions,[16] with a selection of key results using Ni(cod)$_2$, NHC ligands, and toluene as solvent at 100 °C depicted. Unfortunately, attempts to conduct the desired cyclization using SIPr·HCl (**7**) in the presence of NaO*t*Bu were unsuccessful (entry 1). However, upon switching to NHC precursor **8**, the Mizoroki–Heck product **6** was obtained, albeit in modest yield (entry 2). Further improvements were seen when benzimidazolium salt **9** was employed,[17] which gave rise to the desired product **6** in 76% yield (entry 3). We also probed the Ni-to-ligand ratio and found that employing a 1:1 ratio of Ni(cod)$_2$ to **9** (rather than a 1:2 ratio) led to diminished yields (entry 4). Efforts to optimize the Ni loading were also undertaken. Although using 10 mol% Ni(cod)$_2$ gave the desired product (entry 5), the use of 15 mol% Ni(cod)$_2$ gave excellent yields (entry 6) and was found to be more generally effective across a range of substrates studied subsequently. During the course of our

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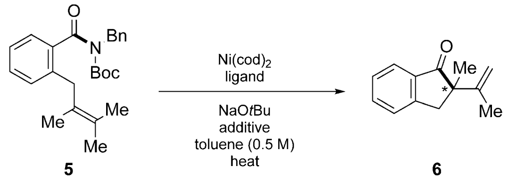
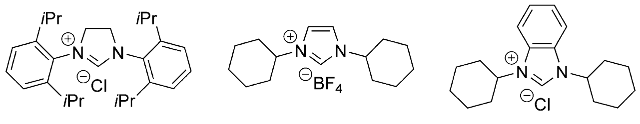
Table 1: Evaluation of ligand effects and reaction conditions for the conversion of **5** into Mizoroki–Heck cyclization product **6**, which bears a quaternary center.[a]



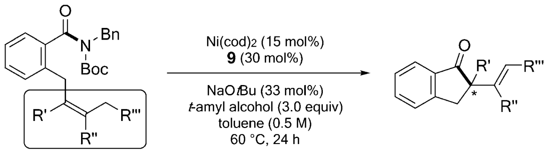


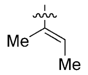
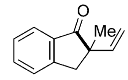
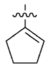
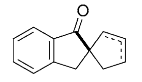
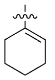
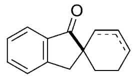
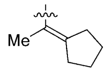
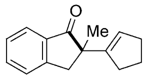
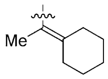
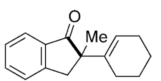
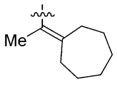
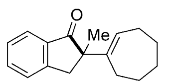
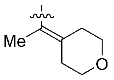
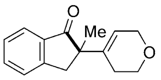
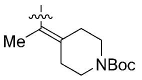
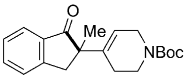
SIPr•HCl (**7**) ICy•HBF$_4$ (**8**) Benz-ICy•HCl (**9**)

Entry	Ni(cod)$_2$ Loading [mol%]	Ligand, Loading [mol%]	Additive	*T* [°C]	Yield [%][b]
1	20	**7**, 40	none	100	0
2	20	**8**, 40	none	100	24
3	20	**9**, 40	none	100	76
4	20	**9**, 20	none	100	67
5	10	**9**, 20	none	100	51
6	15	**9**, 30	none	100	91
7	15	**9**, 30	*t*-amyl alcohol[c]	60	95

[a] Conditions unless otherwise stated: **5** (1.0 equiv, 0.1 mmol), Ni(cod)$_2$ (mol% as shown), **7**–**9** (mol% as shown), toluene (0.5 M), NaO*t*Bu (1.1 × ligand loading) heated at the specified temperature for 24 h in a sealed vial. [b] Yields reflect an average of two experiments and were determined by ^{1}H NMR analysis using hexamethylbenzene as an internal standard. [c] 3.0 equiv of *t*-amyl alcohol was used. cod = bis(1,5-cyclooctadiene).

Table 2: Mizoroki–Heck cyclization of a variety of tri- and tetrasubstituted olefin substrates.



Entry	Alkene	Product	Yield [%][a]
1		 **10**	71[b]
2		 **11**	92[b]
3		 **12**	75[b]
4		 **13**	51
5		 **14**	96
6		 **15**	80
7		 **16**	91
8		 **17**	93

[a] Yields shown reflect the average of two isolation experiments. [b] Reaction performed at 100 °C in the absence of *t*-amyl alcohol.

studies, we also evaluated a series of additives used previously in Ni-catalyzed couplings.[18] These efforts demonstrated that the reaction temperature could be lowered to 60 °C, provided that *t*-amyl alcohol was employed as the additive, to deliver product **6** in 95% yield (entry 7).[19] It should be noted that: 1) Ni-catalyzed Mizoroki–Heck reactions to form quaternary centers are rare,[20] 2) there are no prior examples reported of Ni-catalyzed Mizoroki–Heck reactions involving tetrasubstituted olefins,[21] and 3) decarbonylation products were not observed during reaction development.

Having identified conditions to achieve the nickel-catalyzed cyclization, we evaluated the scope with respect to the tethered alkene (Table 2).[22,23] It was found that a trisubstituted olefin[24] analogue of our parent substrate could be employed to furnish terminal olefin product **10** in 71% yield (entry 1). We also examined substrates in which the trisubstituted olefin was embedded in a ring. Using both 5- and 6-membered ring substrates, the desired Mizoroki–Heck cyclization proceeded smoothly to give the corresponding spirocyclic products **11** and **12**, respectively, as mixtures of olefin isomers (entries 2 and 3).[25] Returning to the more challenging tetrasubstituted olefins, a series of substrates bearing exocyclic olefins were prepared and evaluated. Utilization of a substrate containing a 5-membered ring led to product **13** in 51% yield (entry 4), and the use of substrates containing 6- and 7-membered rings furnished products **14** and **15**, respectively, in good yields (entries 5 and 6). Finally, two heterocyclic substrates were examined. We were delighted to find that our method proved tolerant of a tetrahydropyran and a protected piperidine, giving rise to tricycles **16** and **17**, respectively, in excellent yields (entries 7 and 8).

As shown in Figure 2, the method is also tolerant of substituents on the arene. For example, the use of substrates containing a fluoride or trifluoromethyl group, both of which are critical in medicinal chemistry,[26] gave rise to products **18** and **19**, respectively. A methoxy group was also well tolerated, as shown by the formation of **20** and **21**. As demonstrated by the synthesis of **22** and **23**, substrates bearing a methyl group could also be utilized. In the latter case, it is notable that the presence of a methyl group *ortho* to the tethered alkene did not hinder reactivity.

As a further test, we asked whether this reaction could be performed in a diastereoselective manner (Figure 3). Trisubstituted olefin **24**,[27] which bears an allylic methyl group, was treated under our optimal reaction conditions. This reaction delivered ketone **25** in 80% yield with a 92:8 ratio of diastereomers. Notably, **25** contains vicinal sp^3 stereocenters,

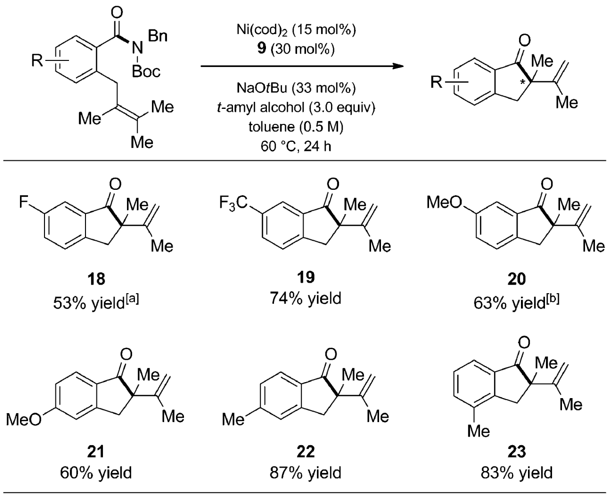


Figure 2. Tolerance of the reaction to substituents on the arene motif. Yields shown reflect the average of two isolation experiments. [a] Yield determined by ^{1}H NMR analysis using hexamethylbenzene as an external standard. [b] Reaction performed at 100 °C in the absence of *t*-amyl alcohol.

both of which are highly substituted. Prior transition-metal-catalyzed methods for the synthesis of 2-vinylindanones[23] have not been demonstrated for the construction of such complexity. The diastereoselectivity seen in the conversion of **24** into **25** can be rationalized by considering the two competing olefin insertion transition states, **TS1** and **TS2**. In both cases, the olefin insertion event is thought to occur via a standard 4-centered transition state, which prompts allylic strain arguments.[28] In **TS1**, A(1,3) strain between the two highlighted hydrogens is minimal and the methyl group rests in a pseudo-equatorial disposition. As such, **TS1** is favorable and leads to the major diastereomer of **25** shown, with the methyl groups residing in a *cis* fashion. On the other hand, the minor diastereomer of **25** (not depicted) is thought to arise from **TS2**, which displays a less favorable A(1,3) interaction between the highlighted hydrogen and the methyl substituent.

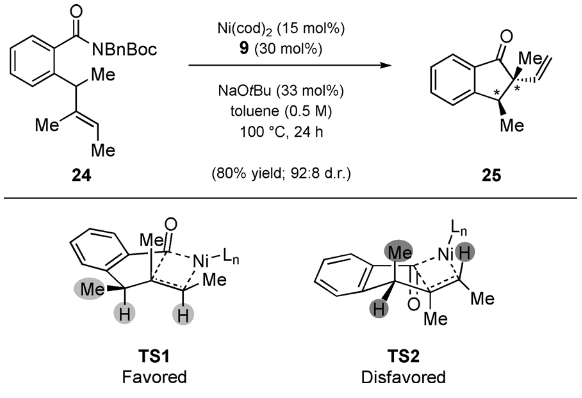


Figure 3. Diastereoselective Mizoroki–Heck cyclization for the introduction of vicinal sp^3 stereocenters. The yield and diastereomeric ratio shown reflect the average of two isolation experiments.

In summary, we have developed a Mizoroki–Heck cyclization of amide derivatives to access ketones containing quaternary centers. The transformation is tolerant of variation on both the alkene and aryl moieties, and most notably, proceeds when using sterically hindered tetrasubstituted olefins. As a result, polycyclic, spirocyclic, and heteroatom-containing products can be synthesized using this method. Moreover, we have demonstrated that a diastereoselective Mizoroki–Heck cyclization proceeds for the controlled formation of an adduct bearing vicinal, highly substituted sp^3 stereocenters. In addition to providing a rare Ni-catalyzed Mizoroki–Heck cyclization method for accessing quaternary centers, as well as the first Mizoroki–Heck cyclization of amide derivatives, our results demonstrate that amides, despite once being viewed as unreactive, can be used as building blocks for the preparation of complex scaffolds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amides · homogeneous catalysis · Mizoroki–Heck reactions · nickel · quaternary centers

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[12] Amide derivatives are considered to be ideally suited for use as synthons in chemical synthesis because of their directing-group ability and stability to a variety of reaction conditions.

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[14] The substrates described in this manuscript were derived from commercially available 2-halobenzoic acid derivatives and readily available allylic electrophiles, either through lithiation/displacement or reductive coupling methods (see the Supporting Information). Reductive couplings: a) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767–1775; b) L. L. Anka-Lufford, M. R. Prinsell, D. J. Weix, *J. Org. Chem.* **2012**, *77*, 9989–10000; c) X. Cui, S. Wang, Y. Zhang, W. Deng, Q. Qian, H. Gong, *Org. Biomol. Chem.* **2013**, *11*, 3094–3097; d) E. C. Hansen, D. J. Pedro, A. C. Wotal, N. J. Gower, J. D. Nelson, S. Caron, D. J. Weix, *Nat. Chem.* **2016**, *8*, 1226–1230.

[15] Other classes of amide derivatives were also evaluated, such as *N*-Me,Ph, *N*-Me,Ts, *N*-Ph,Boc, and *N*-Ph,Ts. However, these efforts either led to no product or the Mizoroki–Heck cyclization product in diminished yields. Similarly, efforts to generate 6- or 7-membered-ring products were unsuccessful.

[16] Extensive variations with respect to the base (e.g., Cs_2CO_3, K_3PO_4, NaH), ligand (e.g., terpyridine, IMes, Benz-I*t*Bu), solvent (DME, DMA, $PhCF_3$), Ni and ligand loadings, and temperature were explored.

[17] NHC precursors **7**–**9** are commercially available.

[18] Additives such as morpholine, aniline, Et_2NH, and 1-hexanol were also tested. Of all the additives examined, *t*-amyl alcohol proved most successful. Use of alcohols as additives in Ni-catalyzed cross couplings: M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, *135*, 3303–3306.

[19] a) Using entry 7 conditions, cyclized product **6** was obtained in 74% yield. Product **6** is volatile as described in the Supporting Information. b) Product **6** could also be obtained in comparable yield through Mizoroki–Heck cyclization of the *N*-*n*Bu,Boc derivative of **5**, thus demonstrating that this method is not restricted to *N*-benzyl amide derivatives.

[20] Ni-catalyzed Mizoroki–Heck cyclization of aryl halides, albeit without tetrasubstituted olefins: J.-N. Desrosiers, L. Hie, S. Biswas, O. V. Zatalochnaya, S. Rodriguez, H. Lee, N. Grinberg, N. Haddad, N. K. Yee, N. K. Garg, C. Senanayake, *Angew. Chem. Int. Ed.* **2016**, *55*, 11921–11924; *Angew. Chem.* **2016**, *128*, 12100–12103, and references therein.

[21] Examples of Mizoroki–Heck reactions involving tetrasubstituted olefins: a) S. A. Shuler, G. Yin, S. B. Krause, C. M. Vesper, D. A. Watson, *J. Am. Chem. Soc.* **2016**, *138*, 13830–13833; b) J. H. Seo, P. Liu, S. M. Weinreb, *J. Org. Chem.* **2010**, *75*, 2667–2680; c) P. Liu, J. H. Seo, S. M. Weinreb, *Angew. Chem. Int. Ed.* **2010**, *49*, 2000–2003; *Angew. Chem.* **2010**, *122*, 2044–2047; d) M. M. Abelman, T. Oh, L. E. Overman, *J. Org. Chem.* **1987**, *52*, 4130–4133; e) A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman, M. J. Sharp, *J. Am. Chem. Soc.* **2005**, *127*, 18054–18065.

[22] 2-Vinylindanones bearing quaternary stereocenters can also be synthesized through Pd- or Ni-catalyzed α-vinylation of lithium enolates: a) J. Huang, E. Bunel, M. M. Faul, *Org. Lett.* **2007**, *9*, 4343–4346; b) M. Grigalunas, T. Ankner, P.-O. Norrby, O. Wiest, P. Helquist, *Org. Lett.* **2014**, *16*, 3970–3973; c) M. Grigalunas, T. Ankner, P.-O. Norrby, O. Wiest, P. Helquist, *J. Am. Chem. Soc.* **2015**, *137*, 7019–7022; d) A. Chieffi, K. Kamikawa, J. Ahman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897–1900.

[23] A substrate containing a phenyl (Ph) group at the R′ position was also tested, but was deemed unreactive.

[24] This substrate was employed as a 7:1 mixture of *E*/*Z* olefins.

[25] See the Supporting Information for details.

[26] a) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.

[27] This substrate was employed as a 4:1 mixture of *E*/*Z* olefins.

[28] Based on calculated rotational energies for conformers of 3-methyl-1-butene and allylic strain arguments, **TS2** is estimated to be roughly 0.7 kcal mol^{-1} higher in energy than **TS1**. A review: R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841–1860.

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Communications

Homogeneous Catalysis

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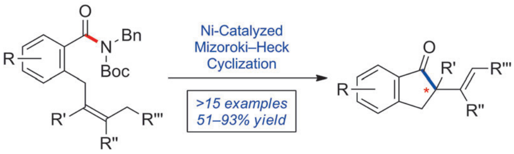
Mizoroki–Heck Cyclizations of Amide Derivatives for the Introduction of Quaternary Centers



Adding complexity: A non-decarbonylative Mizoroki–Heck reaction of Boc-activated amide derivatives is reported. The transformation relies on the use of nickel catalysis and proceeds using sterically hindered tri- and tetrasubstituted olefins to give products containing quaternary centers. The results demonstrate that amide derivatives can be used as building blocks for the assembly of complex scaffolds.